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Air pollution and childhood asthma

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The prevalence of childhood asthma and allergies has dramatically increased worldwide during the last decades, but the etiology of this phenomenon is still not well understood. Asthma is generally less common in developing countries than developed ones but its prevalence is growing up faster as they become more westernized. The etiology of asthma is complicated including a broad spectrum of various determinants as genetic, environmental and lifestyle factors. Increasing trend of asthma prevalence cannot be explained only by genetic changes in the population – evidently, it requires several generations to occur. Thus the understanding of the role of environmental factors and gene-environment interactions could be crucial to explain asthma epidemics [1, 2].

A number of epidemiological studies indicate the critical role of exposure to environmental tobacco smoke (ETS) in the prevalence of wheezing, bronchial hyperresponsiveness and asthma in children [1, 3]. The results of population-based cohort study in Finland (60 000 children enrolled) showed that the risk of asthma amongst children at 7 years of age increased in a dose-dependent manner during pregnancy [4]. Several systematic reviews and meta-analyses (systematic quantitative reviews) provide a convincing evidence of a positive relationship between parental smoking and childhood asthma development with the increasing risk from 21% up to 85% [1, 3]. Maternal smoking may act through epigenetic mechanisms by altering DNA methylation patterns, histone

modifications and expression of miRNAs [2]. Interestingly, even tobacco smoking habit of grandmother can create increased risk of asthma development in grandchildren delivered in the far future [5]. Moreover, combined exposure to tobacco smoke and environmental air pollution may induce synergistic effect on asthma and allergy development by significant hypermethylation of interferon -gamma (IFN γ) promoter in T effector cells and FOXP3 transcription factor in T regulatory cells [6].

Principal component of air pollution is particulate matter (PM). PM is categorized based on size and consists of PM₁₀ that are 10 μ m in diameter or less, fine PM_{2.5} — they have an aerodynamic diameter of 2.5 μ m or less and ultrafine particles (UFPs) and nanoparticles — defined as particles 100 nm in diameter or less. The distinction between UFPs and nanoparticles lies in their origin (natural substances or industrial by-products vs. engineered molecules). Nanoparticles are not classified as air pollution [7].

PM are of specific importance because of their ability to carry a variety of hazardous chemical compounds. PM air pollution is a mixture of solid and liquid particles differed not only in size but also chemical composition and distribution of chemicals within the particle, and physical features as surface and shape. Size-selecting sampling of PM is necessary to establish the relevance to the penetration to the airways (PM₁₀) and to the bloodstream (fine and ultrafine particles) and deposition in the lungs [8].

The chemical composition of PM is extremely important from toxicological and epigenetical point of view. For example prenatal exposure to polycyclic aromatic hydrocarbons (PAH), also contented in PM, is linked to methylation of the acyl-coenzyme A synthetase long-chain family member 3 (ACSL3) and thus increased the risk of childhood asthma. *In utero* the same exposure was associated with hypermethylation within the IFN γ promoter. Hypermethylation of IFN γ promoter and hypomethylation of interleukin 4 promoter in CD4+ T cells due to ultrafine diesel exhausted particles (DEP) exposure has been also observed in the animal model [2]. Diesel exhaust exposure can induce the changes in methylation of the FOXP3 transcription factor and impaired T-regulatory function [9]. The effect of air pollution on the genome has been also observed in the epidemiological study. Survey conducted in two regions of Czech Republic with different air pollution levels showed a significant influence of air pollution on DNA methylation profiles in school children with and without asthma [10].

A number of studies and meta-analyses showed that high level exposure to indoor PM is associated with impairment of lung function parameters, the incidence of wheezing and childhood asthma exacerbations [1, 3, 11]. Much less studies concerned the relationship between indoor PM exposure and onset of asthma in children and the possible connection has not been yet surely established [11]. It should be noted that indoor-originated PM is mixed with outdoor pollutants and both of them are present in the indoor air. Thus the separation of negative health effects due to only indoor PM is very difficult or even impossible to obtain in the population-based studies [7].

Birth cohort studies are the best study design to examine the impact of childhood air pollution exposure on development of asthma and allergies [7, 11]. A systematic review and meta-analyses performed by Bowatte et al. showed that increased longitudinal childhood exposure to PM_{2.5} and black carbon was associated with increasing risk of childhood asthma. Level of exposure to PM_{2.5} was positively connected with sensitization to aero- and food allergens. Traffic-related pollution was also related to the prevalence of eczema and hay fever. However, the authors of the review underlined substantial variability across analyzed studies [11].

Little is known about the meaning of PM constituents in the natural history of childhood asthma. Gehring et al investigated the effects

of PM constituents on asthma, allergy and lung function in children until the age of 11–12 years. 3.702 children participated in a prospective birth cohort study. Questionnaire-reported asthma and hay fever and measurements of allergic sensitization were linked with annual average exposure of copper, iron, potassium, nickel, sulphur, silica, vanadium and zinc in PM₁₀ and PM_{2.5} at birth addresses and current addresses. The authors concluded that PM constituents as iron, copper and zinc may increase the risk of allergy and asthma in schoolchildren. Metals mentioned above are not allergenic and have no adjuvant effects and the exposure measurement results may reflect poorly regulated non-tailpipe road traffic emissions and may be the markers of the presence of different substances or parameters non-measured in the study [12]. The results of the study are only seemingly in conflict with the results of an excellent recently published multicenter study on exposure to the air pollutions and childhood asthma prevalence: the Escape project. The aim of the study was to examine the effects of six traffic-related air parameters (nitrogen dioxide, nitrogen oxide, PM₁₀, PM_{2.5}, total suspended particulates, and PM_{2.5} absorbance) on childhood asthma and wheeze prevalence in five European birth cohorts. No significant association between asthma prevalence and air pollution exposure has been found at age 8–10 years and exposure at the birth address [13]. The analysis of the results of both studies emphasizes the necessity of further research on relationship between chemical and physical features of PM and childhood asthma and allergy.

Indoor exposure to nitrogen dioxide, product of high temperature combustion derived mainly from the gas cooking appliances, has been reported historically as a risk factor of the development of childhood asthma by many authors but recent population-based studies performed with the proper methodology produced conflicting results [1, 3]. The explanation of the inconsistency may be due to different exposure pattern of the studied population. Average exposure to this noxious agent were measured daily or weekly but short term peak exposures were dropped. The results of animal studies suggest that repeated, short time exposures to high concentrations of nitric dioxide are much more harmful than continuous exposure to the low or medium concentration of this agent exceeding limit values [14]. Nitrogen oxide probably can display important role in modulation of the epigenetic profile of the genome from asthma point of view. Increased beta-2 adrenergic recep-

tor (ADRB2) methylation has been observed in children with severe asthma exposed to indoor nitric oxide. ADRB2 is a well-known important regulator of bronchial smooth muscle tone [2].

In summary, substantial heterogeneity of the results of epidemiological surveys suggests necessity of long-term studies investigating lifetime outcomes and more detailed analysis of the environmental exposure [1]. Greater understanding of the most “responsible” pollutants should be done in relation to sources (traffic vs. low emission), chemicals and susceptible populations [15]. In this issue of PiAP you will find an original paper from India on the influence of indoor air pollution on the risk of asthma in children [16].

Conflict of interest

The authors declare no conflict of interest.

References

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